

Control Theory for Biologists

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Chapter 1

Introduction to Modeling

1.1 Build a Simulation Model

Water Tank Model

Figure 1.1 shows two water tanks. The first tank is fed with water at a rate Q_1 ($\text{m}^3 \text{s}^{-1}$). This tank drains into a second tank at a rate Q_2 which in turn drains to waste at a rate Q_3 . The second tank has an additional feed of water flowing in at a rate Q_4 . The height of the water level in each tank is given by h_1 and h_2 respectively. Each tank has a cross sectional area A .

The rate of change in the volume of water in a given tank is the rate at which the water enters minus the rate at which it leaves. For example for the first tank we have:

$$\frac{dV_1}{dt} = Q_1 - Q_2$$

If we want the equation in terms of the rate of change of height then we need to recall that $V = Ah$, that is:

$$\frac{dV}{dt} = A \frac{dh}{dt}$$

so that:

$$\frac{dh}{dt} = \frac{Q_1 - Q_2}{A}$$

Using Torrielli's Law we know that the rate of water flowing out of a given tank, i , is equal to:

$$Q_i = K_i \sqrt{h}$$

Where K_i is a constant related to the resistance of the output pipe. Therefore for the first tank we have:

$$\frac{dh}{dt} = \frac{Q_1 - K \sqrt{h}}{A}$$

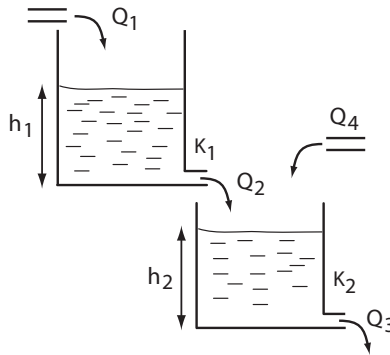


Figure 1.1: Water Tank Model

Given this information, answer the following questions:

- Plot the rate of outflow, Q_2 , as a function of the height of water, h_1 at a given resistance, K_1 .
- Assuming that Q_1 and Q_4 are fixed, and we start with both tanks empty, what do you expect to happen over time as water flows in?
- Write out the differential equations (ODEs) that describe the rate of change in the tank water levels, h_1 and h_2 .

- d) Build a computer model of the tank system, assign suitable values to the parameters in the model and run the simulation to plot the height of water in the tanks over time. Assume both tanks are empty at time zero.
- e) Investigate the effect of increasing and decreasing the resistance parameters, K_1 and K_2 on the model.

1.2 Models and Systems

In the previous section we built a quantitative model of a water tank system but what exactly is a model?

A **model**, according to the Oxford English Dictionary is:

“A simplified or idealized description or conception of a particular system, situation, or process, often in mathematical terms, that is put forward as a basis for theoretical or empirical understanding, or for calculations, predictions, etc.”

This definition embodies a number of critical features that defines a model, the most important is that a model represents an **idealized description**, a simplification, of a real world process. This may at first appear to be a weakness but simplification is usually done on purpose. Simplification is important because it allows us to comprehend the essential features of a complex process without being burdened and overwhelmed by unnecessary detail. In the water tank model we assumed for example that as the water flowed from each tank, any resulting water turbulence had only a negligible effect on the system dynamics.

Models come in various forms including verbal, written text, visual, mathematical and others. Biology, particular molecular biology, has

a long tradition of using visual models to represent cellular structure and function; one need only look through a modern textbook to see instances of visual models on every page. Visual models have been immensely useful at describing complicated biological processes but are limited in their scope. A more interesting way to describe models is to use mathematics, a language designed for logical reasoning. Mathematical models are useful in biology for a number of reasons, but the three most important are increased **precision**, **prediction**, and the capacity for **analysis**. Analysis can be carried out either by simulation or by analytic means. Although visual models can be used to make predictions, the kinds of predictions that can be made are limited. The use of mathematical models opens up whole new vistas of study which visual models simply can not match.

One word that has been used but has been undefined is the word “System”. Here we define what is mean by the system:

System: The part of the Universe we are interested in studying with a defined boundary and set of processes within.

Open, Closed, and Isolated Systems

Like many other scientific studies, modeling divides the world into two parts, the system and the surroundings. The system is that part of the universe we wish to focus our attention. This might be a single enzyme reaction, a pathway, a single cell, an organ, or an entire multicellular organism. The surroundings includes everything else. The boundary between the system and the surroundings can have different properties which determines whether the system is **isolated**, **closed** or **open** (See Figure 1.2). All living systems are open because they exchange energy and matter with their surroundings. An isolated system is one where nothing can enter or leave. Such system can only be approximated as it is very difficult to completely isolate a part of the Universe. A thermos flask can be considered

an isolated system, although an imperfect one. A closed system is one that can exchange energy with the surroundings. Any mass in the system is isolated from the surroundings. An example of a close system is the bomb calorimeter.

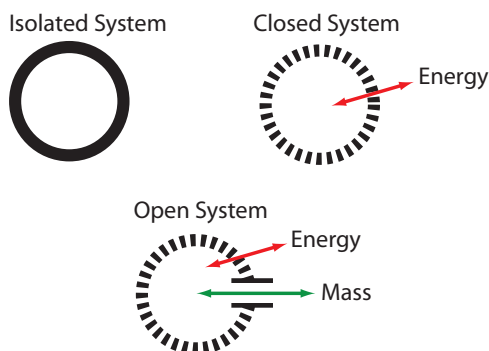


Figure 1.2: Open and Closed Systems.

Class Question 1

For each of the following systems, decide whether the system is isolated, closed or open. Comment on the nature of the surroundings.

- A system represented by a mechanical clock slowly winds down in a room controlled by a thermostat.
 - A car engine running idle in the open air.
 - A bacterial culture is grown in batch and kept in a sealed and insulated chamber.
-

What Makes a Good Model?

What makes a good model? There are a range of properties that a good model should have, but probably the most important are **accuracy**, **predictability** and **falsifiability**.

▷ A model is considered **accurate** if the model is able to describe current experimental observations, that is a model should be able to reproduce the current state of knowledge.

▷ A **predictive** model should be able to generate insight and/or predictions that are beyond current knowledge. Without this ability a model is considerably less useful, some would even suggest useless.

▷ Finally, a model should be **falsifiable**. By this we mean that a model cannot be proved true only disproved. The only discipline where statements can be actually be proved to be true or false is mathematics. Starting with a set of axioms, mathematicians derive theorems that can be shown beyond any doubt to be true or false. In contrast, scientific models based on observations cannot be proved correct. This is because it is simply not possible to test every possible circumstance in which the model may apply. Instead we are left with two options 1) We falsify a model by finding one observation that the model fails to predict. When this happens the model must be changed or abandoned. For example, the hypothesis, RNA is never transcribed into DNA can be falsified simply by finding one instance where it happens (e.g. the life cycle of the HIV virus)¹. Although the idea of falsifying a model is appealing, in practice it is not often used. Instead models are devised and used based on the degree of confidence we have in them, which leads to the second option; 2) We find observations that are consistent with the model. In this case our confidence in the model to make useful predictions increases. Finding observations that are consistent with a model or match a particular prediction is called **model validation**. The word validate may suggest that we are suggesting that the model is correct but this is not true. A validated model is simply one where our confidence in a model's ability to predict and provide insight has increased. This is an extremely important point that is often missed

¹The theory of common descent is falsifiable. If an entire population of fossilized rabbits were found in a precambrian formation, the theory would be in serious trouble.

by both the popular media and lay population.

There are other attributes of a model that are desirable but not essential, these include **parsimonious** and **selective**. A parsimonious model is a model that is as simple as possible, but no simpler. Occam’s infamous razor states that “Entities should not be multiplied beyond necessity” and argues that given competing and equally good models, the simplest is preferred. Finally, since no model can represent everything in a given problem, a model must be **selective** and represent those things most relevant to the task at hand.

Steps in Building Model

To summarize we can break down the approach to building a model into at least four stages.

- Define the system boundaries.
- Define the simplifying assumptions.
- Invoke physical laws to describe the system processes.
- Test (validate) the model against experimental data.

Different Ways to Represent Physical Models

The tank model described in section 1.1 was built using a set of ordinary differential equations (ODEs) and solutions to these equations were obtained using a digital computer. There are however many other ways to build and solve a physical model. Table 1.1 lists some of the more common and interesting approaches that people have used in the past to construct and simulate models.

Table 1.1: Different ways to construct and solve physical models

Electrical Circuits	General purpose analog computer [5]
---------------------	-------------------------------------

	WWII V2 guidance system [18] Neuromorphic electronics [1, 4]
Mechanical and Fluid	Slide rule [15] Curta [8] Tide predicting machine [17] Computing projectile trajectories [14] Differential analyzer (solves ODEs) [9] Antikythera mechanism (planetary motion) [6] Water tanks - MONIAC economic model [12]
Purely Mathematical	Algebraic Equations Linear differential equations Linear difference equations Partial differential equations Probabilistic models Statistical models
Digital Computer	Solving ODEs and PDEs Agent based models (multicellular systems) Cellular automata [7] Emergent systems (Ant models) [10] Fractal models [11] Neural networks [13]

1.3 Model Variables and Parameters

Model Variables

One of the first decisions to make when developing a model is to identify the external (the causes) and internal variables (effects).

The internal variables of the system are often termed the **state vari-**

ables or **dynamic variables** and will change in time as the system evolves. The values of the state variables are determined by the model or system. In an experiment involving living cells the state variables will often be concentrations of molecules and ions, voltages across membranes, ion currents, mass flows etc.

In contrast to the internal variables, the external variables are fixed and in principle are under the complete control of the experimenter. Often the external variables are clamped to some fixed values (*cf.* voltage clamp). The external variables are also called **boundary variables** because they are considered to be at the boundary of the system and the rest of the universe. In an experiment involving living cells the external variables will often be concentrations of nutrients in the medium, the level of oxygen or the concentrations of externally applied drugs or growth factors.

Physically, external variables are clamped by some kind of buffering mechanism. The buffering mechanism can simply be a large external reservoir so that any exchange of mass between the system and the external reservoir has a negligible effect on the external concentration. Alternatively there may be active mechanisms maintaining an external concentration. A classic example of active maintenance of an external variable is the voltage clamp used in electrophysiology. Finally, external concentrations may simply be slow moving compared to the timescale of the model so that over the study period, the external concentrations change very little. A typical example of the latter is the study of a metabolic response over a timescale that is shorter than gene expression. This permits a modeler to study a metabolic pathway without considering the effect of changes in gene expression.

The separation between the internal and external variables depends ultimately on practical considerations and the particular questions that the experimenter and modeler wish to answer. However, once the choice is made, the separation is strictly adhered to during the course of a study. This means for example that the environment sur-

rounding the physical system will, **by definition**, be **unaffected** by the behavior of the system. If for some reason parts of the environment do change then these parts should be considered part of the system.

Forcing Functions

As described earlier, it is common to make sure that the surroundings do not change during the duration of the study. For example we might make sure that the pH remains constant by using a buffer solution. The key point is that the experimenter has complete control over the experiment. In some cases it is useful for an experimenter to change the surrounding conditions in a controlled fashion. For example, he/she might slowly increase the concentration of an administered drug or make a step change in a variable such as the concentration of an enzyme. In systems theory such controlled changes are often called forcing functions.

Model Parameters

As described previously the state variables are quantities that evolve in time and the boundary variables are concentrations or voltages that are clamped by the observer or under the control of a forcing function. There is a third set of quantities which are often called the **system parameters**. These include the various kinetic constants and enzyme activity factors whose values are determined by a combination of thermodynamic, physical or genotypic properties. Some system parameters will appear in the reaction rate laws as kinetic constants, others will be related to physical characteristics such as the volume of the system (assuming the volume is constant during the study period). As with boundary variables, the system parameters are in principle under the control of the experimenter and are not a function of the model itself. One can imagine for example

changing kinetic constants via site directed mutagenesis or changing enzyme activities by altering promoter efficiencies. The actual choice of system parameters in any particular model will depend on physical limitations and the question being considered by the researcher.

Class Question 2

For the water tank model described in section 1.1, write out the variables and parameters of the system. Identify the boundary parameters.

Mathematical Descriptions of Models

Table 1.1 lists the many different ways in which a model can be represented and simulated. However one thing they all have in common is that the models are expressed first in mathematical form. The form of this expression determines how the model will be constructed and how it will be solved or simulated. In particular decisions must be made about how the variables and parameters in the system are best described. For example the model variables can be described either using **discrete** or **continuous** variables. For example the change in the level of water in a tank is more reasonably described using a continuous variable such as the height. On the other hand it might be more realistic to describe the dynamics of lion predation on the Serengeti using a discrete model where individual lions can be represented. It might not make much sense to refer to 34.67 lions in a model. The choice of whether to use a discrete or continuous description depends entirely on the system being studied and the questions posed.

Another important categorization is whether the model should be represented in a **deterministic** or **stochastic** form. A deterministic model is one where if we repeated the simulation using the same starting conditions we would get exactly the same result again. That

is the future state of the model is completely determined by its initial starting point. The model of the water tanks filling up is an example of a deterministic model. In contrast, each time we ran a computer simulation of a stochastic model we would get a slightly different outcome even though the starting conditions are the same.

A **discrete variable** is one that cannot take on all values within a given numeric range. For example, the number of aeroplanes in the sky at any one time is a discrete number. In statistics this is generalized further to a finite set of states, such as true/false or combinations in a die throw.

Continuous variables can assume all values within a given numeric range. For convenience we will often represent a measurement as a continuous variable. For example we will often use a continuous variable to represent the concentration of a solute as it is unwieldy to refer to the concentration of a solute as 5,724,871,927,315,193,634,656 molecules per liter.

The reason for this is that each step in the simulation is determined by one or more random processes. To give an example, modeling lion predation on the Serengeti could be modeled as a stochastic process. It is not guaranteed that a Lion will catch its prey every time, instead there is a probability it will succeed. To model this process the computer simulation would throw a die to determine whether the Lion had succeeded or not. Repeatedly running such a simulation again would naturally give a slightly different outcome because the die throws would be different in each run.

A **deterministic model** is one where a given input will always produce the same output. For example, in the equation, $y = x^2$, setting x to 2 will always yield the output 4.

A **stochastic model** is one where the processes described by the model include a random element. This means that repeated runs of a model will yields slight different outcomes.

We can now therefore classify a model as a combination of the above attributes. The water tank model uses a deterministic, continuous approach. The lion model might use a discrete and stochastic approach. In this book we will be primarily concerned with deterministic and continuous models. Table 1.2 shows the four combinations and example where each combination might be appropriately used.

Type	Example
Continuous/Deterministic	Projectile motion
Continuous/Stochastic	Brownian motion
Discrete/Deterministic	Large population dynamics
Discrete/Stochastic	Small population dynamics

Table 1.2: Examples of different kinds of model

Class Question 3

How you would describe each of the following systems in terms of how you might model them?

- 1. A game of chess
- 2. Two teams playing American Football
- 3. A forest fire
- 4. Gene regulation in a bacterium
- 5. The beating of a healthy heart

6. A tornado
 7. Growth of a tumor
 8. Upper atmosphere chemistry
 9. A digital computer
 10. Electron flow through a single transistor
 11. A population of cells from which emerges a cancerous cell
 12. Metabolism
 13. The swimming of a single E. coli through water
-

1.4 Classification of Models

In addition to classifying models as discrete/continuous and deterministic/stochastic there are additional properties of models that can be used to categorize them (Table 1.3).

1. Linear or Non-Linear
2. Dynamic or Static
3. Time invariant or time dependent
4. Lumped or distributed parameter models

Table 1.3: Additional categories of models

Dynamic and Static Models

A static model is one where the variables of the system do not change in time. For example, a circuit made up of only resistors can be modeled as a static system because there are no elements in the circuit that can store or dissipate charge thus currents and voltages are considered instantaneous without any time evolution. Most interesting model are dynamic.

Time Invariant Systems

A time invariant model is one where the model does not explicitly depend on time. This means that given a time invariant model, running the model at $t = 0$ or $t = 10$ makes no difference to the time evolution of the model. If a parameter of the system depends on time then the model is called time dependent. An example of a time dependent model is where we apply a drug in the form of a pulse and the duration of the pulse depends on when the drug is administered. An example of a time dependent non-biological model is a parking lot where the price of a ticket depends on the time of day. We will have more to say about time invariant systems in a later chapter when we will talk about linear time invariant systems (LTI).

Lumped and Distributed Parameter Models

Many complex models can be approximated with a single number. For example we often describe a resistor using a single value, its resistance. In reality, the resistor has a length, a diameter and a chemical composition. The resistance is a function of all these properties that make up the resistor. We could model the resistor by slicing up the resistor into many small compartments and compute the resistance as a systemic property. In the former case we have what is called a lumped parameter model, in the second case a distributed parameter model.

Linear and Nonlinear Systems

We will discuss linear and non-linear systems in much more detail in Chapter ?? but we can say at this stage that a linear system is one where the output changes in proportion to the inputs. That is, doubling the input will result in a doubling of the output.

Box 1.0 Review of basic electricity

v = Voltage i = Current R = Resistance
 C = Capacitance Q = Charge

Ohms Law: $v = R_i$

Capacitor Law: $Q = C v$ or $v = \frac{1}{C} Q$

In addition, the charge on a capacitor is given by:

$$q = \int i dt$$

combining the two previous relations and differentiating yields:

$$i = C \frac{dv}{dt}$$

Resistors in series/parallel:

In series: $R = \sum R_i$

In parallel: $1/R = \sum 1/R_i$

Capacitors in series/parallel:

In series: $1/C = \sum 1/C_i$

In parallel: $C = \sum C_i$

Kirchhoff's Laws - KCL and KVL

KCL: At a node $\sum i_{in} = \sum i_{out}$ or $\sum i_k = 0$

KVL: Around a cycle $\sum v_k = 0$

1.5 Electrical Models

We are now going to briefly look at electrical systems and how they can be used to model physical systems.

Class Question 4

Given the following resistor network, determine the voltage V_o .

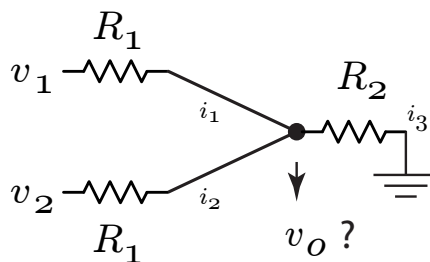


Figure 1.3: Resistor Network

When you've derived the relation for v_o , assume $R_2 \gg R_1$ and then infer what calculation could be done with the circuit.

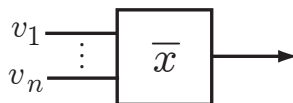


Figure 1.4: Block that computes the average of inputs V_1 to V_n .

Class Question 5

Show that the resistive circuit in Figure 1.6 can be used to compute a voltage times a constant.

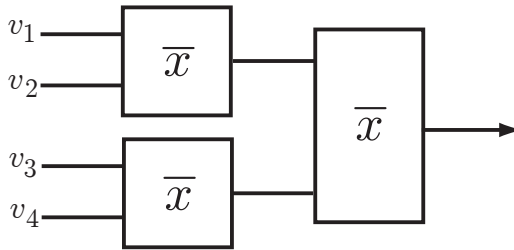


Figure 1.5: Combining computational blocks

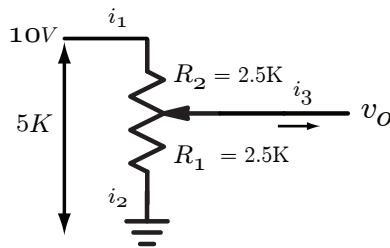


Figure 1.6: Circuit to multiply an input voltage by a constant.

Class Question 6

What is the problem with all these circuits that could make them potentially poor at computing?

There are many other kinds of circuits one can build using passive components. Two of the most common are the integrator and differentiator circuits (Figure 1.7). Integrators carry out the mathematical operation:

$$\int v dt$$

while differentiators carry out the operation:

$$\frac{dv}{dt}$$

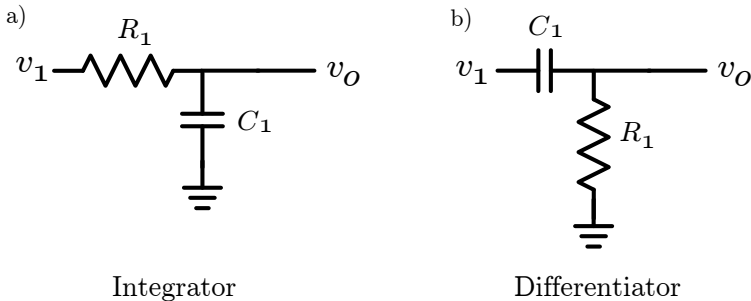


Figure 1.7: Integrator and differentiator circuits

Assignment 1

Watch the YouTube videos: RC Integrator Circuit² and RC Differentiator Circuit³ (Figure 1.7).

As with the summer and multiplier circuits these passive circuits suffer from loading issues and are not particularly practical as computational circuits.

Avoiding the Loading Issue

The way to avoid the loading issues described in the last section is to use some kind of buffer circuit such as an **Op Amp**. Op Amps, or

²<http://www.youtube.com/watch?v=JbpR5nGu0Gg>

³<http://www.youtube.com/watch?v=qtrYd0uJzyA>

operational amplifiers, are the workhorse of many analog circuits, they can be purchased very cheaply with varying characteristics to suit a myriad of different applications.



Figure 1.8: Common 741 Op Amp. Image from Jameco Electronics, cost \$0.25 each

In their basic form, an op amp has five terminals. Two of these terminals are used to supply power to the circuit and are not normally shown when drawing op amp circuits. The remaining three terminals represent two input and one output terminal. The two input terminals are designated the inverting and non-inverting terminals respectively. In diagrams the two input terminals are often indicated with a plus and a minus sign (Figure 1.9)

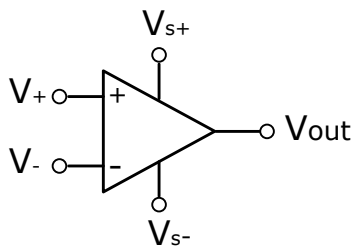


Figure 1.9: Symbol for an Op Amp. V_{s+} and V_{s-} are the positive and negative supply voltages. V_+ and V_- are the inverting and non-inverting inputs.

Basic Properties of an Op Amp

An Op Amp amplifies the difference in voltage between the positive and negative input terminals, that is:

$$v_o = A(v_+ - v_-)$$

where A is the so-called gain of the amplifier. In real op amps, the gain is usually of the order of at least 10^5 . For an op amp operating with a supply voltage of 15 volts, the difference in voltage between the two input terminals cannot be more than $120 \mu V$ in order to avoid saturation of the amplifier. This means that an op amp on its own is of little practical value because the slightest difference in voltage at the input terminals will cause the op amp to saturate. When applied to real problems op amps are almost always used with some kind of feedback circuit.

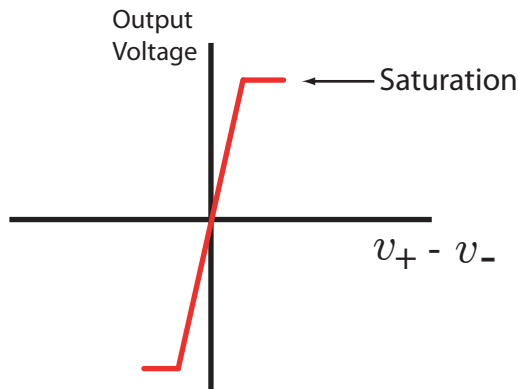


Figure 1.10: Basic Op Amp Response.

Although the basic op amp is essentially a very high-gain amplifier, it has certain other properties which make it extremely useful. These properties are listed below:

1. The resistance (or impedance) into the input terminals is extremely high.
2. The resistance (or impedance) of the output terminal is extremely low.

The high impedance on the input terminals means that an op amp will impose hardly any load on the circuit it is connected to. The input resistance will often be of the order of at least a mega ohm, often more.

A low impedance on the output terminal of the order of 70 ohms or less, means that attaching loads to the op amp will have hardly any effect on the output voltage. As a result of these properties, op amps are ideal components to use as buffering circuits for the computational circuits described in the previous section.

To illustrate a simple example, consider the non-inverting amplifier shown in Figure 1.11. From the circuit we can determine the currents, i_1 and i_2 from the voltage drops across, R_1 and R_2 , that is:

$$i_1 = \frac{v_F - 0}{R_1} \quad i_2 = \frac{v_O - v_F}{R_2}$$

Note that the ground voltage is 0. In an ideal op amp, the amount of current flowing into positive and negative inputs is zero, this means that the two currents, i_1 and i_2 must be equal, therefore it must be true that:

$$\frac{v_F}{R_1} = \frac{v_O - v_F}{R_2} \quad \Rightarrow \quad \frac{v_F}{R_1} + \frac{v_F - v_O}{R_2} = 0$$

Another property of an op amp is that the output voltage is equal to the gain, A , times the difference in the input voltage:

$$v_O = A(v_I - v_F)$$

Rearranging this yields:

$$v_F = v_I - \frac{v_O}{A} \quad (1.1)$$

Inserting v_F into the current equation gives:

$$\frac{v_I - \frac{v_O}{A}}{R_1} + \frac{v_I - \frac{v_O}{A} - v_O}{R_2} = 0$$

The final property of an op amp is that the gain, A , is very large, ideally infinite, therefore the above equation simplifies to:

$$\frac{v_I}{R_1} + \frac{v_I - v_O}{R_2} = 0$$

This can now be rearranged to solve for v_O :

$$v_O = v_I \left(1 + \frac{R_2}{R_1} \right)$$

The remarkable thing about this result is that the gain of the op amp, A , has vanished. Computationally this circuit will take an input voltage, v_I , and multiply it by a scaling factor. The only disadvantage to the non-inverting circuit is that the scaling will be greater than one, it is no possible to scale v_I by a factor < 1 .

More importantly, given the high input and low output impedance, the circuit doesn't suffer the loading issues of a simple resistive circuit. Combining op amps with resistive/capacitive circuits is a common way to make analog computational modules that can be easily connected together without the modules interfering with each other.

Equation 1.1 is of interest because it helps to understand the operation of the circuit intuitively. Given that the gain, A , of the op amp is huge we can approximate equation 1.1 to:

$$v_I = v_F$$

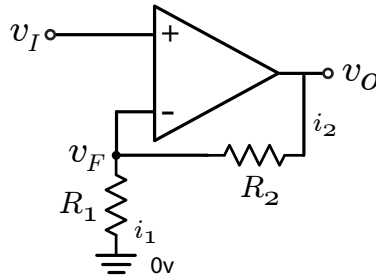


Figure 1.11: Non Inverting Op Amp Circuit.

This tells us that whatever the input voltage, v_I is, v_F will match it. In order for this to happen, as the input voltage changes v_I the op amp must be going through some kind of dynamic change so that v_F will match any change in v_I . The explanation is simple but crucial to understanding the operation of the circuit.

First we must recall that an op amp is a difference amplifier, that is $v_O = A(v_+ - v_-)$, or $v_O = A(v_I - v_F)$. Imagine we increase v_I above v_F , this means the difference $(v_I - v_F)$ increases which in turn is amplified resulting in an increase in v_O . If v_O increases then part of this is passed back via the resistor R_2 to v_F so that v_F **increases**. If v_F increases, the difference $(v_I - v_F)$ decreases, which in turn reduces the rise in v_O . The feedback cycle continues until v_F converges to v_I at which point the circuit reaches a steady state, that is v_O stops changing and $v_I = v_F$.

Assignment 2

Using the same approach to what was used in the non-inverting amplifier (Figure 1.12), derive the relationship between the input and output voltage for the inverting amplifier.

1) Show that the inverting amplifier behaves like a voltage divider (??) while at the same time inverting the signal.

2) Show that the voltage at v_F is zero. Using the explanation that $v_I = v_F$ for the non-inverting op amp, explain why v_F is zero in an inverting op amp.

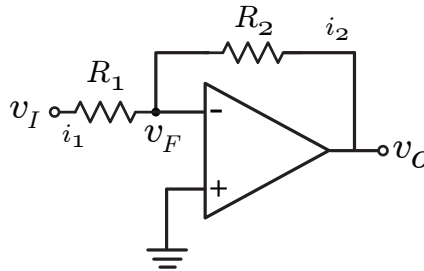


Figure 1.12: Non-Inverting Op Amp Circuit.

Figure 1.13 shows three computational op amp circuits, a summer, an integrator and a differentiator.

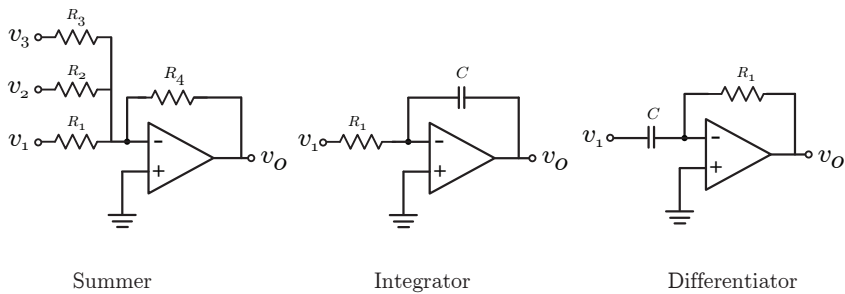


Figure 1.13: Three different computational circuits made from op amps. Note the similarity with the non-op amp circuits in Figure 1.7.

1.6 Block Diagrams

In many text books, block diagrams are used to illustrate a model. We already seen that electrical circuits can be used perform various computations and these can be represented in the form of block symbols. Figure 1.14 shows some common block symbols found in the literature. Using these symbols let us draw a block diagram that represents the differential equation and its solution:

$$\frac{dS_1}{dt} = -kS_1$$

Solving a differential equation involves integration. Therefore the first block to consider is the integral block. The input to this block will be the derivative, dS_1/dt and the output will be S_1 . However S_1 appear as a negative term in the differential equation, $-kS_1$, therefore we will also invert S_1 at the same time. Once we have $-S_1$ we only need to add a ‘multiply by a constant block’ to multiply $-S_1$ by the constant k to obtain the value of dS_1/dt . This final operation closes the loop. Figure 1.15 illustrates the complete block diagram.

From the block diagram we could construct this device out of suitably sired op amps such that the electrical circuit would solve the differential equation. Before the advent of the digital computer, such ‘analog’ computers were common place and were use to solve a variety of problems in science and engineering. One of the advantages of an analog computer is that they are very fast and can be operated in a life mode such that it is possible to interact with the model in real time and the analog computer will automatically adjust the solution.

However, with the advent of fast and particularly cheap digital computers the need for analog computer has declined although there is increasing interest to use some of the ideas in a new field called

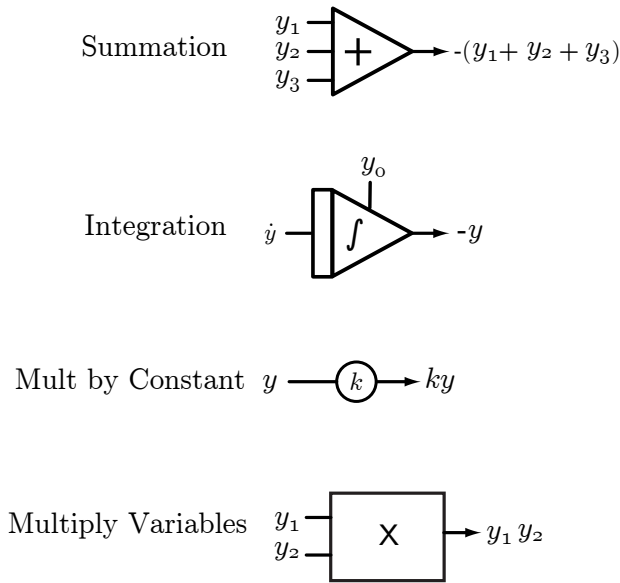


Figure 1.14: Common Block Symbols

Neuromorphic electronics [1, 4] where the aim is to recreate brain like computational systems from electrical analog circuitry.

Assignment 3

Draw a block diagram of the following system of two differential equations.

$$\frac{dS_1}{dt} = -k_1 S_1$$

$$\frac{dS_2}{dt} = k_1 S_1 - S_2$$

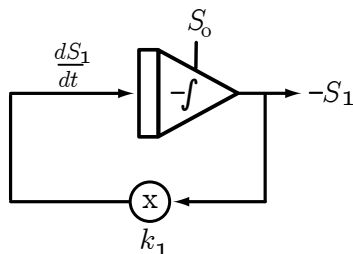


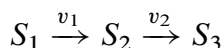
Figure 1.15: Analog System to Solve, $\frac{dS_1}{dt} = -k_1 S_1$

$$S_1(t) = S_1(0) e^{-k_1 t}$$

$$S_2(t) = \frac{k_1}{k_2 - k_1} S_1(0) \left(e^{-k_1 t} - e^{-k_2 t} \right)$$

1.7 Digital Computer Models

We now turn to the use of the programmable digital computer for modeling physical systems. Modern digital computers are programmable machines that can manipulate binary numbers. As such they are very adept at handling problems involving numerical processing. There are a great variety of computer software packages that have been written specifically to solve ordinary differential equations both algebraically and numerically. Consider then the following two consecutive chemical reaction system involving three chemical species, S_1 , S_2 and S_3 .



We assume that each chemical reaction is governed by simple mass action kinetics so that the reaction rates, v_1 and v_2 are given by:

$$v_1 = k_1 S_1 \quad v_2 = k_2 S_2$$

We can write down a simple mathematical model that describes the time evolution of the three species by invoking the conservation of mass. That is:

$$\frac{dS_1}{dt} = -k_1 S_1$$

$$\frac{dS_2}{dt} = k_1 S_1 - k_2 S_2$$

$$\frac{dS_3}{dt} = k_2 S_2$$

In this case the model is simple enough that we can derive the analytical solution for this model. Assuming that at time zero, both S_2 and S_3 are at zero concentration, then it can be shown that:

$$S_1(t) = S_1(0) e^{-k_1 t}$$

$$S_2(t) = \frac{k_1}{k_2 - k_1} S_1(0) \left(e^{-k_1 t} - e^{-k_2 t} \right)$$

$$S_3(t) = S_1(0) \left(1 - \frac{k_2 e^{-k_1 t} - k_1 e^{-k_2 t}}{k_2 - k_1} \right)$$

In the majority of cases it is not possible to derive such an analytical solution and we must therefore fall back on using a computational model. To do this we must find a suitable software application that can solve differential equations. The plot shown in Figure 1.16 was obtained from Jarnac (www.sbw-app.org) but similar plots could be obtained using Matlab.

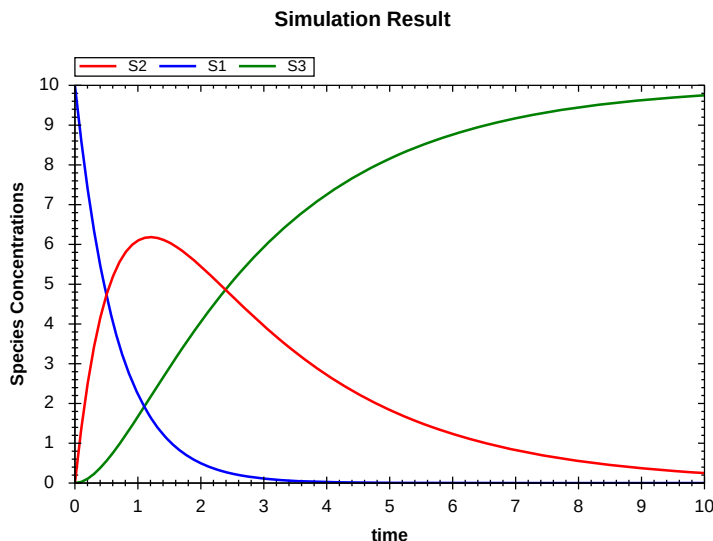


Figure 1.16: Computer Simulation of two Consecutive Chemical Reactions. $S_1(0) = 10, k_1 = 1.5; k_2 = 0.4$

Assignment 4

Obtain the same plot shown in Figure 1.16 using Matlab or Python.

1.8 Dimensions and Units

Variables and parameters that go into a model will be expressed in some standard of measurement. In science the recognized standard for units are the SI units. These include units such as the *meter* for length, *kilogram* for mass, *second* for time, *Joules* for energy, *kelvin* for temperature and the *mole* for amount. The mole is of particular importance because it is a means to measure the number

of particles of substance irrespective of the mass of substance itself. Thus 1 mole of glucose is the same amount as 1 mole of the enzyme glucose-6-phosphate isomerase even though the mass of each type of molecule is quite different. The actual number of particles in 1 mole is defined as the number of atoms in 12 grams of carbon-12 which has been determined empirically to be 6.0221415×10^{23} . This definition means that 1 mole of substance will have a mass equal to the molecular weight of the substance, this makes it easy to calculate the number of moles using the following relation

$$\text{moles} = \frac{\text{mass}}{\text{molecular weight}}$$

The concentration of a substance is expressed in moles per unit volume and is usually termed the molarity. Thus a 1 molar solution means 1 mol of substance in 1 litre of volume.

Dimensional Analysis

Dimensional analysis is a simple but effective method for uncovering mistakes when formulating kinetic models. This is particularly true for concrete models where one is dealing with actual quantities and kinetic constants. Conceptual models are more forgiving and don't usually require the same level of attention because they tend to be simpler.

Amounts of substance is usually expressed in moles and concentrations in moles per unit volume (mol l^{-1}). Reaction rates can be expressed either in concentrations or amounts per unit time depending on the context (mol t^{-1} , $\text{mol l}^{-1} \text{t}^{-1}$).

Rate constants are expressed in differing units depending on the form of the rate law, the rate constants in simple first order kinetics are expressed in per unit time (t^{-1}), while in second order reactions the rate constant is expressed per concentration per unit time ($\text{mol}^{-1} \text{t}^{-1}$).

In dimensional analysis, units on the left and right-hand sides of expressions must have the same units (or dimensions). There are certain rules for combining units when checking consistency in units. Only like units can be added or subtracted, thus the expression $S + k_1$ cannot be summed because the units of S are likely to be $\text{mol } l^{-1}$ and the units for k_1 , t^{-1} . Even something as innocent looking as $1 + S$ can be troublesome because S has units of concentration but the constant value '1' is unit-less. Quantities with different units can be multiplied or divided with the units for the overall expression computed using the laws of exponents and treating the unit symbols as variables.

Class Question 7

Determine the overall units for the expression, $k_1 S / K_m$ where the units for each variable are $k_1 (t^{-1} l)$, $S (\text{mol } l^{-1})$ and $K_m (\text{mol } l^{-1})$.

In exponentials such as e^x , the exponent term must be dimensionless, or at least the expression should resolve to dimensionless, thus e^{kt} is permissible but e^k is not if for example k is a first-order rate constant. Trigonometric functions will always resolve to dimensionless quantities because the argument will be an angle which can always be expressed as a ratio of lengths which will by necessity have the same dimension.

1.9 Approximations

By their very nature, models involve making assumptions and approximations. The best modelers are those who can make the most shrewd and reasonable approximations without compromising a model's usefulness. There are however some kinds of approximations which are useful in most problems, these include:

- Neglecting small effects.
- Assuming that the system environment is unchanged by the system itself.
- Replacing complex subsystems with lumped or aggregate laws.
- Assuming simple linear cause-effect relationships where possible.
- Assuming that the physical characteristics of the system do not change with time.
- Neglecting noise and uncertainty.

Neglecting small effects. This is the most common approximation to make. In many studies there will always be parts of the system that have a negligible effect on the properties of the system, at least during the period of study. For example, the rotation of the earth, the cycle of the moon or the rising and setting of the sun will most likely have negligible influence on our system. Assuming of course we are not studying circadian rhythms.

Assuming that the system environment is unchanged by the system itself. This is a basic assumption in any study. The minute a system starts to affect the environment we have effectively extended the system boundaries to include more of the environment. It will often be the case that the interface between the environment and the system will not be perfect so that there will be some effect that the system has on the environment. So long as this effect is small we can assume that the environment is not affected by the system.

Replacing complex subsystems with lumped or aggregate laws. Lumping subsystems is a commonly used technique in simplifying cellular models. The most important of these is the use of aggregate rate laws, such as Michaelis-Menten or Hill like equations to

model cooperativity. Sometimes entire sequences of reactions can be replaced with a single rate law.

Assuming simple linear cause-effect relationships. In some cases it is possible to assume a linear cause-effect between an enzyme reaction rate and the substrate concentration, this is especially true when the substrate concentration is below the K_m of the enzyme. Linear approximations make it much easier to understand a model.

Physical characteristics do not change with time. A modeler will often assume that the physical characteristics of a system do not change, for example the volume of a cell, the values of the rate constants or the temperature of the system. In many cases such approximations are perfectly reasonable.

Neglecting noise and uncertainty. Most models make two important approximations. The first is that noise in the system is either negligible or unimportant. In many non-biological systems such an approximation might be quite reasonable. However biological systems are particulate in nature and operate at the molecular level. As a result, biological systems are susceptible to noise generated from thermal effects as a result of molecular collisions. For many systems the large number of particles ensures that the noise generated in this way is insignificant and in many cases can be safely ignored. For some systems such as prokaryotic organisms, the number of particles can be very small. In such cases the effect of noise can be significant and therefore must be included as part of the model.

1.10 Behavior

We can classify the behavior of systems in to three broad categories, thermodynamic equilibrium, steady state or transient. The steady state can be further classified into stable or unstable steady states. For example, if we pick biochemical systems as our example then:

Thermodynamic Equilibrium In this state the concentrations of reactants and products show not net change over time; in addition, the rates of all forward and reverse reactions are equal. This means that at thermodynamic equilibrium there is no net movement of mass from one part of the system to another and not net dissipation of energy. In thermodynamics, equilibrium is the state that maximizes the entropy of the system.

Steady State At steady state, the concentrations of reactants and products show not net change over time; however, unlike thermodynamic equilibrium there is a net flow of mass or energy between the system and the environment. At steady state the system will continually dissipate entropy to the external environment while the entropy level of the system itself remains constant.

Transient State Under a transient state, a system will be moving from either one steady state to another or from a steady state to thermodynamic equilibrium.

1.11 Software for Solving ODEs

There are many software tools available for solving ordinary differential equations. We can split the list into open source and proprietary commercial tools. Of the commercial tools Matlab (<http://www.mathworks.com>) and Mathematica (<http://www.wolfram.com>) are well known. Matlab is a numerical computing environment with significant strengths in matrix manipulation and plotting. For solving differential equations, Matlab offers a variety of solvers including traditional Runge-Kutta (ode45 and ode23) and solvers specifically designed for stiff systems based on the Gear method (ode15s). All these solvers implement an adjustable step size algorithm so that the execution proceeds most efficiently. A more

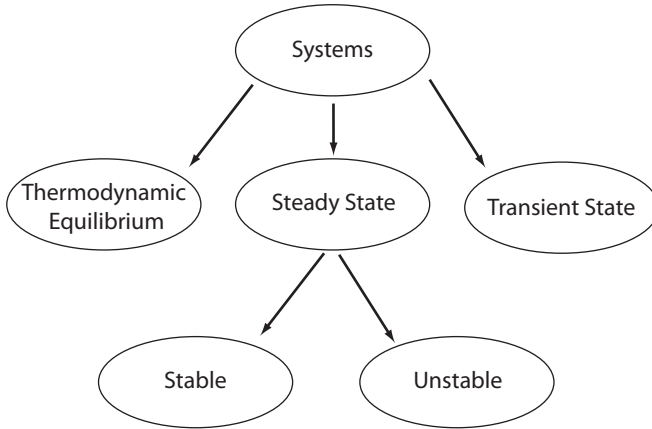


Figure 1.17: Classification of System Behavior

detailed discussion of different kinds of solvers and how they work will be given in Chapter ???. Figure 1.18 illustrate a simple Matlab script for solving a set of two ordinary differential equations. Figure 1.19 shows the same simulation but using Mathematica instead.

Both Matlab and Mathematica are however expensive to purchase, therefore many researchers have either written their own solvers or use publicly available software libraries.

There are free Matlab like tools such as Octave⁴, SciLab⁵, Euler⁶ and Yorick⁷ that can be successfully used. There is also considerable support for solving ODEs from the popular scripting language Python⁸. In addition to these there are specialized tools for modeling specific types of physical systems. For example, Jarnac⁹ has

⁴<http://www.gnu.org/software/octave/>

⁵<http://www.scilab.org/>

⁶<http://euler.sourceforge.net/>

⁷<http://yorick.sourceforge.net/>

⁸<http://www.python.org/>

⁹www.sbw-app.org

specific support for describing chemical or biochemical networks.

```
% Solve a systems of ODE's
% Use ODE45
% Model: -> S1 -> S2 ->
% using simple mass-action kinetics

function [dxdt]= odes(t,x)
    dxdt(1) = 3.4 - 2.3*x(1);
    dxdt(2) = 2.3*x(1) - 0.4*x(2);
return

% Set an error tolerance
options = odeset('RelTol',1e-6);

% Initial conditions
Xo = [0;0];

% Timespan
tspan = [0,5];

% Call the solver
[t,X] = ode45(@odes, tspan, Xo, options);

% Plot the results
plot(t,x(1), t,x(2))
legend('S1', 'S2')
```

Figure 1.18: A Matlab script for solving a simple set of differential equations and plotting the results.

Solving the Lorenz Attractor

In this section we will illustrate the use of Matlab and Python to solve the famous chaotic model called the Lorenz system. The

```

NDSolve[{3.4 - 2.3 x1[t] == x1'[t],
        2.3 x1[t] - 0.4 x2[t] == x2'[t],
        x1[0] == 0, x2[0] == 0}, {x1, x2}, {t, 0, 5}]

Plot[Evaluate[{x1[t], x2[t]} /. s], {t, 0, 5},
     PlotRange->All]

```

Figure 1.19: Mathematica script for solving a simple set of differential equations.

Lorenz system is a three variable system of differential equations given by the following:

$$\begin{aligned}\frac{dx}{dt} &= -\sigma x + \sigma y \\ \frac{dy}{dt} &= \rho x - y - yz \\ \frac{dz}{dt} &= -\beta z + xy\end{aligned}$$

The first example illustrates how Matlab can be used to solve the differential equations. To solve differential equations we must first declare a function that computes the right-hand sides of the differential equations and return the derivatives to the caller. This is shown below.

```

function xprime = lorenz(t,x);
% Computes the derivatives of
% the differential equations
sig=10;
beta=8/3;
rho=28;
xprime=[-sig*x(1) + sig*x(2);
        rho*x(1) - x(2) - x(1)*x(3);
        -beta*x(3) + x(1)*x(2)];

```

To solve the Lorenz system, one of the Matlab provided ODE solver routines can be used. In the script below ode45 is used which implements an adaptive step-size Runge-Kutta method (See Chapter ??).

```
>>x0 = [-8 8 27];  
>>tspan = [0, 20];  
>>[t,x] = ode45 (@lorenz, tspan, x0)  
>>plot (t, x)
```

The first line sets up the initial conditions for the three variables, the second up the duration of the simulation, and the third line carries out the actual simulation. The last line plots the data as a graph.

The next example shows how we can use Python to solve the Lorenz system. This relies on the SciPy and NumPy packages. The SciPy package includes a wide variety of numerical methods for solving different kinds of problem. The first part of the script imports the required libraries:

```
import scipy  
from scipy.integrate import odeint  
import numpy  
import matplotlib.pyplot as plt
```

The second part of the script defines the system of differential equations:

```
def lorenz(x, t):  
    sigma = 10  
    rho = 28  
    beta = 8.0/3  
    return [ sigma * (x[1] - x[0]),  
            x[0] * (rho - x[2]) - x[1],  
            x[0] * x[1] - beta* x[2]]
```

Note the indentation of the lines, this is important for Python. Finally we invoke the ODE solver and plot the resulting simulation data.

```
xInitial = [0, 1, 1.05]
t = numpy.arange(0, 30, 0.01)
lorenzSolution = scipy.integrate.odeint(lorenz, xInitial, t)

plt.plot (lorenzSolution)
plt.show()
```

Domain Specific Tools

In addition to tools that can solve differential equations, there are also domain specific tools that allow a user to specify the physical problem in a way that will be more familiar to the user. From such input the software will derive the differential equations automatically. This can help reduce errors in the final equations. Examples of such tools include SPICE [16] for modeling electrical circuits and Jarnac [3] for modeling biochemical networks. In biochemical modeling there are also standard file formats for storing models. The most well know of these is the Systems Biology Markup Language (SBML) [2]. This means that applications that support SBML can access the large number of models available in model repositories such as Biомodels. Many of the example models in this book will be described using Jarnac scripts which can be easily converted to SBML or Matlab. Jarnac is a windows application that offer a wide range of analysis methods for modeling biochemical networks. A simple example is given here:

```
// Define a simple linear chain of reactions
p = defn cell
    $Xo -> S1; k1*Xo - k2*S1;
    S1 -> S2; k3*S1/(k4 + S1);
    S2 -> $X1; k5*S2^2;
end;

// Initialize parameters
p.Xo = 10;
p.k1 = 0.6; p.k2 = 0.4;
```

```
p.k3 = 3.4; p.k4 = 0.1;  
p.k4 = 1.2;  
  
// Carry out simulation and plot results  
// Three arguments = timeStart, timeEnd, numberOfPoints  
m = p.sim.eval (0, 10, 100);  
graph (m);
```

A user manual can be found at www.sbw-app.org.

Exercises

1. Identify the state variables and parameters in the following systems:

- a) A projectile fired from a cannon (Figure 1.20)

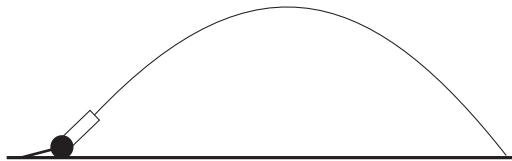


Figure 1.20: Projectile fired from a cannon

- b) An RC circuit acting as a low pass filter (Figure 1.21)
 - c) An ecosystem comprising of a population of rabbits and foxes where the model is base on the Lotka-Volterra system of equations.
 - d) A chemical system based on the Brusselator model.
2. Build and simulate the following models:

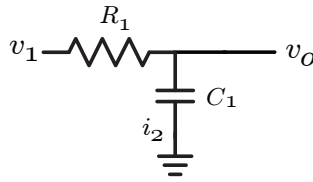


Figure 1.21: RC Circuit

Predator/Prey Models

a) Build a computer model of the predator/prey system described by the Lotka-Volterra system of equations:

$$\frac{d\text{Prey}}{dt} = \text{Prey} \cdot \alpha - \beta \cdot \text{Prey} \cdot \text{Predator}$$

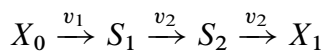
$$\frac{d\text{Predator}}{dt} = \delta \cdot \text{Prey} \cdot \text{Predator} - \gamma \cdot \text{Predator}$$

where α is the growth rate of the prey, β is the rate of predation, γ is the death rate of the predator and δ is the rate of growth in the predator population.

b) Explore how the parameters affect the evolution of the populations

Biochemical Models

Build a computer model of the following simple metabolic pathway:



Assume that the metabolites, X_o and X_1 are fixed. Assume also that v_1 and v_2 are governed by the rate laws:

$$v_1 = E_1(k_1 X_o - k_2 S_1)$$

$$v_2 = E_2(k_3 S_1 - k_4 S_2)$$

$$v_3 = E_3 * k_5 * S_2$$

where E_i is the concentration of the i^{th} enzyme and k_i are the kinetic rate constants.

- a) Write out the variables and parameters of the system.
- b) Write out the differential equations for this system.
- c) Assign arbitrary but realistic values to the various parameters in the model and compute the steady state, that is when $dS_i/dt = 0$. Report the steady state concentrations of S_1 and S_2 .
- d) What is the effect of doubling all E_i by a factor α on the steady state concentrations of S_1 and S_2 ?

Pharmokinetic Models

Figure 1.22 shows a simple compartmental model of what happens to a drug when it is injected intravenously into a patient. The model comprises of three compartments, the blood stream, the liver and the actual site of action. It is assumed that the drug can freely exchange between the liver and blood compartments but that the liver can also irreversibly degrade the drug. In addition some drug is lost by excretion through the kidneys. Finally some drug accumulates irreversibly at the site of action.

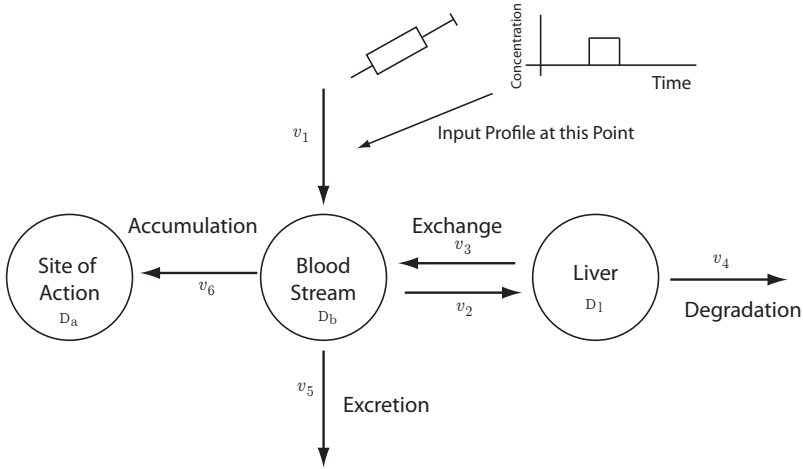


Figure 1.22: Simple model of a drug begin injected and distributed through the body.

We will assume that movement of the drug between compartments obeys simple first order kinetics. For example, the rate, v_2 , at which drug enters the liver is given by $k_2 D_b$ where D_b is the concentration of drug in the blood stream and k_2 is the kinetic constant for the process. The complete list of rates is given below:

$$v_2 = k_2 D_b$$

$$v_3 = k_3 D_l$$

$$v_4 = k_4 D_l$$

$$v_5 = k_5 D_b$$

$$v_6 = k_6 D_b$$

where D_b is the concentration of drug in the blood stream,

D_l the concentration of drug in the liver, and D_a the concentration of drug at the site of action. Using the conservation of mass, three differential equations can be written down that describe the rate of change of drug in each of the three compartments.

Previous pharmacokinetic studies of the drug indicate that the rate constants for the entry and exit of drug to and from the various compartments are given by: $k_2 = 6.12$, $k_3 = 0.2$, $k_4 = 0.45$, $k_5 = 1$, $k_6 = 5$.

All units in seconds. Using a simulation model answer the following question.

Assume that the nurse can inject 1 mM of drug per second into the patient's blood stream. That is, in one second the concentration of drug in the blood stream increases by 1 mM (A little unrealistic perhaps). This is another way of saying that $v_1 = 1 \text{ mM sec}^{-1}$. The nurse can start and stop the injection very quickly such that the profile one observes in the rate at which drug enters the blood looks like a pulse as shown in Figure 1.23.

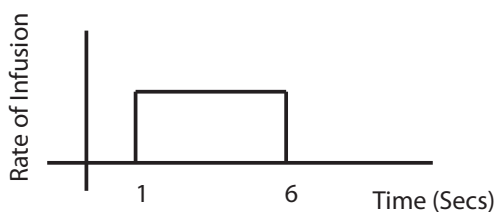


Figure 1.23: Drug Infusion Profile.

Assume that in order for the drug to be effective the concentration at the site of action must reach at least 2.5 mM. If the

concentration of drug in the syringe is 1 mM, use the computer model to roughly estimate the minimum time the injection should last in order for the drug to be effective.

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